REMARKS

Claim 1 has been amended to spedify th hydrochloride salt at at least 4% weight. The basis for the hydrochloride salt is page 7 lines 18-21 or original claim 13. The basis for the "at least 4 weight %..." figure is page 7 lines 8-11 or original claim 12. Corresponding amendments have been made to independent method of making claims 26 and 32.

Claims 2-10, 14, 19, 27 et al. refer to hydrochloride salt to match claim 1.

Claim 11 and 12 have new HCl salt percentages based on page 7 lines 8-11.

Claim 13 has its basis on page 6 line 40 to page 7 line 6.

Claims 14, 16 and 19 are now singly dependent only, so that later multiple dependent claims can depend on them.

Claim 20 has an extra filler feature with added based on page 9 line 4-6.

Claim 22 has an extra binder feature with added based on page 10 lines 10 to 18.

Claim 23 has extra binders with added based on page 10 lines 1-7.

Method claim 33 with specific particle size has added bases on claim 3.

Claim 34 has a grammatical error corrected.

New composition claims 35-50 are supported in the originally-filed specification as follows:

Claim 35 has basis in page 6 line 40 to page 7 line 6.

Claim 36 has basis on page 9 lines 4-6.

Claim 37 and 45 have bases on page 7 lines 23-24, page 8 lines 34-40, and page 9 lines 4-9.

Claim 38 has basis on page 8 lines 34-36.

Claim 39 has basis on page 8 line 41 to page 9 line 2

Claim 40 has basis on page 9 lines 33-37

Claim 41 has basis on page 9 lines 11-15.

Claim 43 has basis on page 9 lines 11-12.

Claim 44 and 46 have bases on page 10 lines 26-30 and lines 36-39.

Claim 47 and 48 have bases on page 11 lines 1-2.

Claim 49 and 50 have bases on page 11 lines 21-22 or original claim 28.

New dependent method claim 51 is based on claim 27 or page 11 lines 16-19, together with: page 8 lines 34-40, page 9 lines 4-9, page 9 lines 11-15, and page 9 lines 33-37 of the specification. as originally filed.

Applicants are of the opinion that the Examiner has misread the prior art. The HCL salt referred to in claim 1 is the present compound hydrochloride.

Obviousness Rejections

Claims 1 – 34 are rejected under 35 U.S.C. 103(a) as being unpatentable ocver WO93/18036 to Gaster et al., in view of Remington's Pharmaceutical Sciences and the International Cosmetic Ingredient Dictonary and Handbook. Applicants respectfully traverse the rejection and assert that the PTO has not met its burden of proving a *prima facie* case of obviousness.

Gaster (WO 93/18036) does disclose on page 7 lines 27-37 that pharmaceutical compositions, containing a compound of formula (I) or salt thereof which encompasses the claimed hydrochloride, "are usually adapted for enteral such as oral, nasal or rectal, or parenteral administration, and as such may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, nasal sprays, suppositories, injectable and infusable solutions or suspensions...." (emphasis supplied).

However, the reference in Gaster to "granules" is submitted to refer to Japanese-style granules, wherein (usually) a spherical bead is coated with excipients and the drug, and the coated granules – rather than tablets - are administered orally directly to the patient. This passage is submitted not to disclose that the present hydrochloride particles themselves are "in granulated form" according to claim 1.

Also, page 8 lines 33-37 of Gaster only appears to say that blending operations are conventional. It does not say that granulation processes (according to claim 1 and method claims 26 and 32) are conventional.

Examiner appears to rely on his citation of Remington's Pharmaceutical Sciences, 18th edition 1990, page 1641, for the alleged teaching that "[t]he most widely used and most general method of tablet preparation is the wet-granulation method". Examiner appears not to have

read the whole chapter, and indeed has not provided the whole chapter in his citation, and in particular has not provided the section on "Direct Compression", so that the whole context of the citation cannot be seen.

Remington's Pharmaceutical Sciences, 16th edition, 1980, Chapter 89 "Tablets, Capsules, and Pills", pages 1553-1584 (to be provided in an Information Disclosure Statement to follow), gives a more complete picture. The same statement about wet granulation quoted above is made on page 1560 (continuing later onto pages 1561-1563), but some disadvantages are immediately mentioned on p.1560 which would discourage the skilled person from using wet granulation, namely:

"Its chief disadvantages are the number of separate steps involved, as well as the time and labour necessary to carry out the procedure, especially on a large scale."

Chapter 89 of Remington's Pharmaceutical Sciences, 16th edition, 1980, relavent pages enclosed, after discussing wet granulation, then discusses dry granulation on p.1563, and "Direct Compression" on pages 1563-1565. Under the "Direct Compression" heading, on page 1563 column 2 last 2 paragraphs, the reference says:

"As its name implies, direct compression consists of compressing tablets directly from the powdered material without modifying the physical nature of the material itself.....

Since the pharmaceutical industry is constantly making efforts to increase the efficiency of tableting operations and to reduce costs by utilizing the smallest amount of floor space and labor as possible for a given operation, increasing attention is being given to this method of tablet preparation."

This direct compression section of Remington's Pharmaceutical Sciences 16th edn, 1980, then concludes on p. 1564 column 2 last paragraph to p. 1565 column 1 first paragraph as follows:

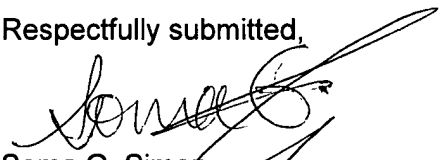
"The gradual improvement of formulation additives and development of mechanical feeding devices for the high-speed rotary tableting machines indicate the acceptance of direct compression as the preferred method for the future. Of all the methods, direct compression is the most adaptable to automation....." (emphasis added).

It is therefore submitted that the skilled pharmaceutical formulation scientist would first try direct compression as the simplest method of first choice, when making tablets. The skilled person would not be motivated to use a composition containing the present hydrochloride in granulated form as claimed in claim 1, or to form the present compound hydrochloride into granules as claimed in independent method claims 26 and 32.

Indeed Gaster page 8 lines 33-36 discloses blending, filling or tabletting, which suggests ther use of direct compression techniques. As suggested in Remington's Pharmaceutical Sciences 16th edn, 1980, p.1560 ("[Wet granulation's] chief disadvantages are the number of separate steps involved, as well as the time and labour necessary to carry out the procedure, especially on a large scale"), the skilled person reading Gaster would not be motivated to use the wet granulation method as it would appear to involve wasteful additional process steps. Thus the cited references teach away from the present invention, rendering the present claims per se non obvious to the skilled artisan.

In view of the above remarks, Applicants are of the view that the present claims are allowable. Reconsideration of this application is requested. Should the Examiner have any questions or wish to discuss any aspect of this case, the Examiner is encouraged to call the undersigned agent at the number below.

Respectfully submitted,



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